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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 191 335 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 14.08.91 (51) Int. Cl.^{5}: C07D 475/04

(21) Application number: 86100944.7

(22) Date of filing: 24.01.86

The file contains technical information submitted after the application was filed and not included in this specification

(54) Preparation process of (6R)-tetrahydro-l-biopterin.

(30) Priority: 28.01.85 JP 12477/85
28.01.85 JP 12478/85

(43) Date of publication of application:
20.08.86 Bulletin 86/34

(45) Publication of the grant of the patent:
14.08.91 Bulletin 91/33

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 153 696

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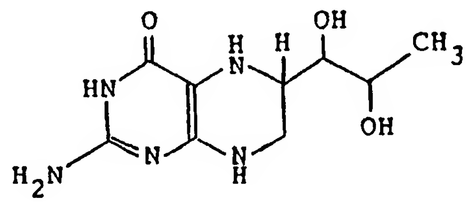
Description

BACKGROUND OF THE INVENTION

Field of the Invention:

This invention relates to a process for the preparation of (6R)-tetrahydro-L-biopterin represented by the following general formula (I):



(I)

more specifically to an industrial preparation process which can provide the 6R form of tetrahydro-L-biopterin in a high proportion.

Discussion of the Background:

Tetrahydro-L-biopterin (hereinafter abbreviated as "BPH_4") contains two isomers, i.e., the 6R and 6S forms depending on the steric configuration of hydrogen at the 6-position [Furrer, H.J., et al.: Helv. Chim. Acta. 62, 2577(1979)].

Of the two stereoisomers, (6R)-BPH_4 is a coenzyme not only for phenylalanine hydroxylases but also for aromatic amino acid hydroxylases.

Its shortage thus leads to scarceness in neurotransmitters such as serotonin, dopamine, noradrenalin and adrenalin, thereby inducing serious neuroses. Malignant hyperphenylalaninemia is a serious and incurable disease which is one of inborn errors of metabolism and cannot be easily treated by any conventional pharmacotherapy. This disease is also known to occur as a result of inhibition of conversion of phenylalanine to tyrosine due to scarceness of (6R)-BPH_4.

It may be contemplated to administer (6R)-BPH_4 for the treatment of malignant hyperphenylalaninemia. For this application, it has been desired to develop a process for economical preparation of this compound with high purity.

As preparation processes of tetrahydro-L-biopterin, it has been known to reduce L-erythro-biopterin enzymatically or chemically. Of these processes, the enzymatic process is unavoidably accompanied by such a drawback that it requires complex facilities and operation, results in a high preparation cost and is hence disadvantageous as an industrial process, although it has a merit that it provides the 6R form only. On the other hand, the chemical process yields a mixture of the 6R form and 6S form, which must be separated subsequently. This separation is however extremely difficult to achieve. No effective method has heretofore been known for their separation.

Accordingly, it has long been desired to develop a process for synthesizing (6R)-BPH_4 in a high proportion, if possible, selectively. However, no satisfactory process has yet been found.

SUMMARY OF THE INVENTION

With the foregoing circumstances in view, the present inventor have carried out an extensive research. As a result, it has been found that the asymmetric ratio R/S can be significantly increased by subjecting L-erythro-biopterin or an acyl derivative thereof to catalytic reduction by a platinum-base catalyst, in the presence of an amine and under specific conditions and moreover, the resultant reaction mixture having such a high R/S ratio facilitates the separation and collection of (6R)-BPH_4, leading to completion of the present invention.

Accordingly, this invention provides a process for the preparation of, (6R)-tetrahydro-L-biopterin (I), which comprises hydrogenating L-erythro-biopterin or an acyl derivative thereof in the presence of an amine or a quaternary ammonium compound other than said biopterin starting material which controls the pH of the reaction medium to within the range of 10 to 13 and a platinum-based hydrogenation catalyst at a H_2

pressure of 0.981 bar (1 kg/cm²) or more, and in the event at least one acyl group remains in the hydrogenated biopterin product obtained,

removing the acyl group by hydrolysis.

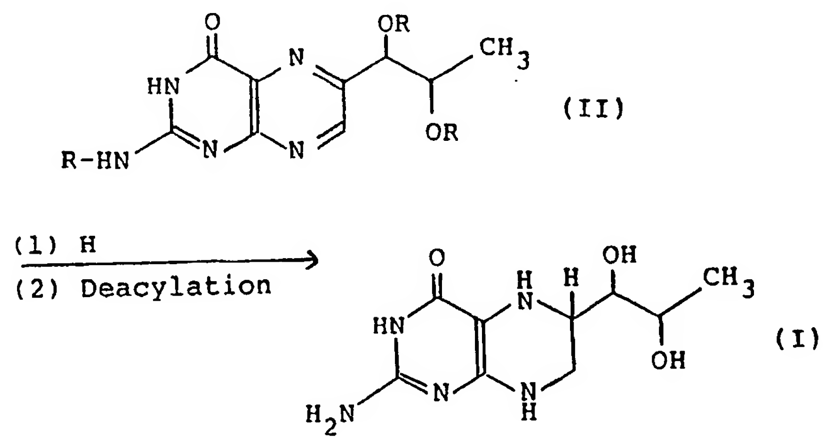
The present invention has succeeded in preparing (6R)-BPH_4, the chemical synthesis of which has heretofore been difficult, at a high asymmetric ratio R/S and moreover with a high yield, and is hence an extremely valuable invention.

Since the process of this invention makes use of an amine as a base, the process is free from admixture of any inorganic salt and can hence provide high-purity crystals with ease. This is another advantageous feature of this invention.

The above and other objects, features and advantages of the present invention will become apparent from the following description and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The reaction of the above process is represented by the following equation:



wherein R means H or acyl group.

In order to practice the present invention, L-erythro-biopterin or its acyl derivative (II) is catalytically reduced with a platinum-base catalyst in water, an alcohol or a mixed water-alcohol solvent, which has in advance been adjusted to pH 10 - 13 with an amine.

As the platinum-base catalyst, may for example be mentioned platinum black, platinum oxide (PtO_2), platinum/carbon (Pt/C), platinum/alumina (Pt/alumina) or the like. Of these, platinum black is particularly preferred in view of yield and asymmetric ratio. On the other hand, illustrative of the alcohol may include methanol, ethanol, methyl cellosolve, ethylene glycol and so on.

As exemplary amines, may be mentioned primary amines such as methylamine, ethylamine, propylamine and cyclohexylamine; secondary amines such as dimethylamine, diethylamine, dipropylamine, piperidine and morpholine; tertiary amines such as trimethylamine, triethylamine and tripropylamine; and quaternary amines such as tetramethylammonium hydroxide, tetraethylammonium hydroxide and tetrapropylammonium hydroxide. These amines may each be added in such an amount that the pH of the resulting reaction solution reaches pH 10 - 13. The presence of such an amine is essential in the present invention. Even if the pH is adjusted to the above-described range by using another base, for example, an inorganic base such as an alkali metal hydroxide, the asymmetric ratio R/S will be low and the yield will also be poor.

The process of this invention may be carried out in accordance with a usual procedure for catalytic reduction. The reaction temperature may preferably be - 10°C to 50°C, while the H_2 pressure may be preferably 1 kg/cm² or higher with 10 to 100 kg/cm² being especially preferred.

In the above manner, (6R)-BPH_4 or its acyl derivative can be obtained with an asymmetric ratio of about 7 or greater. The acyl group or groups are usually removed in the above-described reaction. When some of the acyl groups still remain, they can be removed with ease by hydrolyzing the reaction product with hydrochloric acid or the like. By recrystallizing the thus-obtained reaction product, (6R)-BPH_4 can be isolated and obtained with high purity.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples,

Example 1:

To 95 mℓ of water were added 1.0 g (4.22 mmol) of L-erythro-biopterin and 0.20 g of platinum black, followed by an addition of 10% tetraethylammonium hydroxide to adjust the resultant mixture to pH 12.0. The thus-prepared mixture was charged in an autoclave and reacted with stirring, at an H_2 pressure of 100 kg/cm^2, temperature of 0 - 5°C and revolution rate of 1000 r.p.m. for 20 hours. To the reaction mixture was added 5 mℓ of concentrated hydrochloric acid, followed by removal of the catalyst through filtration. The filtrate was then concentrated under reduced pressure at a bath temperature not higher than 35°C. The residue was recrystallized from a mixed solvent of 3N hydrochloric acid and ethanol. White crystals, (6R)-$BPH_4 \cdot 2HC\ell$ were obtained in an amount of 1.13 g (yield: 85%).

Elementary analysis:

Calculated for $C_9H_{17}C\ell_2N_5O_3$:	C, 34.41; H, 5.45;
N, 22.29. Found:	C, 34.50; H, 5.41; N, 22.58.
Optical rotation $[\alpha]^{25}$:	-6.39° (C, 0.68; 0.1N NCℓ)
^{1}H-NMR ($CD_3OD + D_2O$):	4.10-3.70 (5H, m, H-C(6,7,1',2')), 1.40 (3H, d, J=6Hz, H-C(3')).

Example 2:

To 95 mℓ of water were added 1.0 g (4.22 mmol) of L-erythro-biopterin and 0.20 g of platinum black, followed by an addition of each of the bases shown in Table 1 to adjust the resultant mixture to a prescribed pH level. The thus-prepared mixture was charged in an autoclave and reacted with stirring, at an H_2 pressure of 100 kg/cm^2, temperature of 0 to 5°C and revolution rate of 1000 r.p.m. and for 20 hours. The reaction mixture was added with 5 mℓ of concentrated hydrochloric acid, followed by removal of the catalyst through filtration. The filtrate was then analyzed by high-pressure liquid chromatography to determine the corresponding R/S ratio and the yield of (the R form + the S form). Results are summarized in Table 1.

Conditions for measurement by high-pressure liquid chromatography:

Detector:	ultraviolet absorption photometer (measurement wavelength: 275 nm)
Column:	Partisil-10SCX, 4.5 x 250 mm
Mobile phase:	30 mM ammonium phosphate plus 3 mM ammonium sulfite (pH = 3.0)
Flow rate:	2 mℓ/min.

Table 1

Base	pH	R/S	Yield of R + S forms
Ammonia	11.03	8.2	75
Methylamine	12.24	12.0	81
Ethylamine	11.98	14.3	91
Diethylamine	11.99	8.3	70
Trimethylamine	10.82	9.7	91
Triethylamine	12.01	19.0	95
Triethylamine	12.37	22.0	89
Tetramethylammonium hydroxide	12.02	14.8	93
Tetraethylammonium* hydroxide	12.02	19.0	95
Benzyltrimethyl-ammonium hydroxide	12.16	15.3	95

* Example 1

Table 1 (Cont'd)

Base	pH	R/S	Yield of R + S forms
Cyclohexylamine	12.29	7.7	96
Piperidine	12.05	10.8	78
Morpholine	10.31	7.9	96

Example 3:

The procedure of Example 2 was repeated except that the pH of the starting reaction solution was changed to pH 12 by using triethylamine, diethylamine, ethylamine and tetraethylammonium hydroxide respectively and the reaction temperature and H_2 pressure were changed. Results are shown in Table 2 - Table 5.

Table 2

Base	Triethylamine (pH = 12.0)					
H_2 pressure	1 kg/cm^2		20 kg/cm^2		100 kg/cm^2	
Temperature	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)
0 - 5°C	7.6	88	12.0	94	18.5	94
20°C	5.9	97	10.2	93	16.4	94
40°C	5.5	93	10.6	88	11.3	89

Table 3

Base	Diethylamine (pH = 12.0)					
H_2 pressure	1 kg/cm^2		20 kg/cm^2		100 kg/cm^2	
Temperature	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)
0 - 5°C	7.4	86	10.9	96	14.9	93
20°C	6.5	95	9.7	94	12.8	90
40°C	5.3	87	8.5	88	11.3	89

Table 4

Base	Ethylamine (pH = 12.0)					
H_2 pressure	1 kg/cm^2		20 kg/cm^2		100 kg/cm^2	
Temperature	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)
0 - 5°C	5.5	67	12.1	96	14.3	91
20°C	8.4	97	10.9	96	13.0	96
40°C	6.7	95	10.1	88	11.4	87

Table 5

Base	Tetraethylammonium hydroxide (pH = 12.0)					
H_2 pressure	1 kg/cm^2		20 kg/cm^2		100 kg/cm^2	
Temperature	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)
0 - 5°C	7.2	86	10.7	93	14.5	95
20°C	6.4	96	9.6	95	13.4	94
40°C	5.6	87	12.4	86	10.3	92

Example 4:

To 2 mℓ of each of the solvents shown in Table 6 were added 20 mg of L-erythro-biopterin and 4 mg of platinum black, followed by an addition of the corresponding base given in Table 6 to adjust the resultant mixture to a prescribed pH level. The thus-prepared mixture was charged in an autoclave and reacted at an

H_2 pressure of 100 kg/cm^2 and the corresponding temperature given in Table 6 for 20 hours. The reaction mixture was treated in the same manner as in Example 2 to determine the corresponding asymmetric ratio, R/S, and the yield of (the R form + the S form). Results are summarized in Table 6.

Table 6

Solvent	Base	pH	Reaction temp. (°C)	R/S	(R + S Forms) yield (%)
Methanol	Benzyltrimethyl-ammonium hydroxide	12.68	20	13.2	86
1:1 Mixed solvent of methanol and water	Triethylamine	11.47	0 - 5	13.1	83

Example 5:

To 2 mℓ of water or an organic solvent were added 20 mg of triacetyl-L-erythro-biopterin, 4 mg of platinum black and a base. The thus-prepared mixture was charged in an autoclave and reacted at an H_2 pressure of 100 kg/cm^2 and temperature of 20°C for 20 hours. To the reaction mixture was added 2 mℓ of 3N hydrochloric acid, followed by removal of the catalyst through filtration. Concentrated hydrochloric acid (0.5 mℓ) was added to 1.5 mℓ of the filtrate and the resultant mixture was left over for 3 days to effect deacetylation. The thus-obtained reaction mixture was analyzed by high-pressure liquid chromatography under the same conditions as in Example 2 to determine the R/S ratio and the yield of (the R form and the S form). Results are summarized in Table 7.

Table 7

Solvent	Base	pH	R/S	(R + S Forms) yield (%)
Water	Triethylamine	11.72	9.0	68
Water	Tetraethylammonium hydroxide	12.05	7.4	72
Water	Diethylamine	12.03	7.4	70
Water	Ethylamine	12.01	12.7	87
Methanol	Benzyltrimethylammonium hydroxide	12.63	9.4	65

Example 6:

To 95 ml of water were added 1.0 g (4.22 mmol) of L-erythro-biopterin and 0.20 g of platinum oxide, followed by an addition of 10% tetraethylammonium hydroxide to adjust the resultant mixture to pH 12.0.

The thus-prepared mixture was charged in an autoclave and reacted with stirring, at an H_2 pressure of 100 kg/cm^2, temperature of 0 - 5°C and revolution rate of 1000 r.p.m. and for 20 hours. The reaction mixture was added with 5 mℓ of concentrated hydrochloric acid, followed by removal of the catalyst through filtration. The filtrate was then concentrated under reduced pressure at a bath temperature not higher than 35°C. The residue was recrystallized from ethanol. The crystalline matter was dissolved in 3N hydrochloric acid and the resultant solution was treated with activated carbon. The activated carbon was filtered off, the filtrate was concentrated, and the residue was recrystallized from a mixed solvent of 3N hydrochloric acid and ethanol to obtain 0.98 g of (6R)-BPH_4•2HCℓ as white crystals.

Elementary analysis:

Calculated for $C_9H_{17}Cl_2N_5O_3$: C, 34.41; H, 5.45; N, 22.29. Found: C, 34.48; H, 5.53; N, 22.20.
Optical rotation $[\alpha]^{25}$: -6.51° (C, 0.68; 0.1N HCℓ)
^{1}H-NMR ($CD_3OD + D_2O$): 4.1-3.7 (5H, m, H-C(6,7,1',2')), 1.40 (3H, d, J=6Hz, H-C(3')).

Example 7:

Water (2 mℓ), L-erythro-biopterin (20 mg), a catalyst (4 mg) and triethylamine were added to adjust the pH to 12. The thus-prepared mixture was charged in an autoclave and reacted with stirring, at an H_2 pressure of 100 kg/cm^2 and temperature of 0 - 5°C for 20 hours. To the reaction mixture was added 5 mℓ of concentrated hydrochloric acid, followed by removal of the catalyst through a microfilter. The filtrate was then analyzed by high-speed liquid chromatography to determine the asymmetric ratio, R/S, and the yield of (the R form + the S form). Results are summarized in Table 8.

Conditions for measurement by high-pressure liquid chromatography:

Detector: ultraviolet absorption photometer (measurement wavelength: 275 nm)
Column: Partisil-10SCX, 4.5 x 250 mm
Mobile phase: 30 mM ammonium phosphate plus 3 mM ammonium sulfite (pH = 3.0)
Flow rate: 2 mℓ/min.

Table 8

Catalyst	Asymmetric ratio, R/S	(R + S forms) Yield (%)
PtO_2	9.9	92
5% Pt/C	8.6	81
5% Pt/alumina	8.4	87
PdO (comparison)	3.3	14
5% Rh/C (comparison)	2.9	19

Example 8:

Using KOH, triethylamine, diethylamine, ethylamine and tetraethylammonium hydroxide as bases, the pHs of the reaction mixture were adjusted to 12 respectively. The procedure of Example 7 was repeated at 0 to 5°C and an H_2 pressure of 100 kg/cm^2 by using ptO_2, 5% pt/C and 5% pt/alumina as catalysts respectively. Results are summarized in Table 9 to Table 11.

Table 9

	PtO_2	
	Asymmetric ratio, R/S	(R + S forms) yield (%)
Ethylamine	8.1	89
Diethylamine	8.2	90
Triethylamine	9.9	94

Table 9 (Cont'd)

	PtO_2	
	Asymmetric ratio, R/S	(R + S forms) yield (%)
Tetraethylammonium hydroxide	9.7	84
KOH (comparison)	5.5	83

Table 10

	5% Pt/C	
	Asymmetric ratio, R/S	(R + S forms) yield (%)
Diethylamine	6.8	75
Triethylamine	8.6	81
Tetraethylammonium hydroxide	8.1	83
KOH (comparison)	4.1	88

Table 11

	5% Pt/alumina	
	Asymmetric ratio, R/S	(R + S forms) yield (%)
Triethylamine	8.4	87
Tetraethylammonium hydroxide	8.0	82

Example 9:

The procedure of Example 7 was repeated except that platinum oxide was used as a catalyst, triethylamine was employed to adjust the pH to 12, and the reaction temperature and H_2 pressure were changed. Results are summarized in Table 12.

Table 12

H_2 pressure	1 kg/cm^2		20 kg/cm^2		100 kg/cm^2	
Temperature	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)	R/S	(R + S forms) yield (%)
0 - 5°C	3.8	75	7.4	91	9.9	94
20°C	3.3	56	7.2	93	8.1	90
40°C	4.1	87	5.8	88	7.5	85

Example 10:

L-Erythro-biopterin (20 mg) and platinum oxide (4 mg) were added to each of the solvents shown in Table 13, followed by adjustment with the corresponding base given in the same table to the prescribed pH. The resultant mixture was charged in an autoclave and then reacted at an H_2 pressure of 100 kg/cm^2 and

the corresponding temperature given in Table 13 for 20 hours. The reaction mixture was treated in the same manner as in Example 7 to determine the asymmetric ratio, R/S, and the yield of (the R form + the S form). Results are also given in Table 13.

Table 13

Solvent	Base	pH	Temperature	R/S	(R + S Forms) yield (%)
Methanol	Benzyltrimethylammonium hydroxide	12.6	20°C	8.7	85
1:1 Mixture of methanol and H_2O	Triethylamine	11.5	0 - 5°C	7.9	82

Example 11:

To 2 mℓ of water or an organic solvent were added 20 mg of triacetyl-L-erythro-biopterin, 4 mg of platinum oxide and a base. In an autoclave, the thus-prepared mixture was reacted at an H_2 pressure of 100 kg/cm^2 and temperatures of 0 to 5°C for 20 hours. The reaction mixture was added with 2 mℓ of 3N hydrochloric acid, followed by removal of the catalyst through filtration. Concentrated hydrochloric acid (0.5 mℓ) was added to 1.5 mℓ of the filtrate and the resultant mixture was left over for 3 days to effect deacetylation. The thus-obtained reaction mixture was analyzed by high-pressure liquid chromatography under the same conditions as in Example 7 to determine the R/S ratio and the yield of (the R form and the S form). Results are summarized in Table 14.

Table 14

Solvent	Base	pH	R/S	(R + S Forms) yield (%)
Water	Triethylamine	11.76	11.9	85
Methanol	Benzyltrimethylammonium hydroxide	12.52	8.2	88

Claims

1. A process for the preparation of (6R)-tetrahydro-L-biopterin, which comprises: hydrogenating L-erythro-biopterin or an acyl derivative thereof in the presence of an amine or a

quaternary ammonium compound other than said biopterin starting material which controls the pH of the reaction medium to within the range of 10 to 13 and a platinum-based hydrogenation catalyst at a H_2 pressure of 0.981 bar (1 kg/cm²) or more, and in the event at least one acyl group remains in the hydrogenated biopterin product obtained,
removing the acyl group by hydrolysis.

2. The process of Claim 1, wherein the hydrogenation is conducted under an elevated pressure of 10 to 100 kg/cm².

3. The process of Claim 1, wherein the platinum-based catalyst is selected from the group consisting of platinum black, platinum oxide, platinum/carbon and platinum/alumina.

4. The process of Claim 1, wherein the hydrogenation is conducted in water, an alcohol or a mixed water-alcohol solvent.

5. The process of Claim 1 , wherein the hydrogenation is conducted in water.

6. The process of Claim 1, wherein the hydrogenation is conducted at a temperature in a range of from -10° C to 50° C.

7. The process of Claim 1, wherein the hydrolysis is conducted with hydrochloric acid.

8. The process of Claim 1, wherein the amine is selected from the group consisting of methylamine, ethylamine, propylamine, cyclohexylamine, dimethylamine, diethylamine dipropylamine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, tetramethylammonium hydroxide, tetraethylammonium hydroxide and tetrapropylammonium hydroxide.

Revendications

1. Procédé de préparation de (6R)-tétrahydro-L-bioptérine, gui comprend :

- l'hydrogénation de la L-érythro-bioptérine, ou d'un dérivé acylé de celle-ci, en présence d'une amine ou d'un composé ammonium quaternaire autre que ladite matière de départ bioptérine, qui contrôle le pH du milieu réactionnel pour qu'il se situe à l'intérieur de la plage allant de 10 à 13, et d'un catalyseur d'hydrogénation à base de platine, à une pression d'H_2 de 0,981 bar (1 kg/cm²) ou davantage ; et dans le cas ou au moins un groupe acyle reste dans le produit de bioptérine hydrogéné obtenu,
- l'élimination du groupe acyle par hydrolyse.

2. Procédé selon la revendication 1, dans lequel l'hydrogénation est effectuée sous une pression élevée de 10 à 100 kg/cm².

3. Procédé selon la revendication 1, dans lequel le catalyseur à base de platine est choisi dans le groupe constitué par le noir de platine, l'oxyde de platine, le platine/carbone et le platine/alumine.

4. Procédé selon la revendication 1, dans lequel l'hydrogénation est effectuée dans l'eau, un alcool ou un solvant mixte eau-alcool.

5. Procédé selon la revendication 1, dans lequel l'hydrogénation est effectuée dans l'eau.

6. Procédé selon la revendication 1, dans lequel l'hydrogénation est effectuée à une température se situant dans une plage allant de -10° C a 50° C.

7. Procédé selon la revendication 1, dans lequel l'hydrolyse est effectuée avec de l'acide chlorhydrique.

8. Procédé selon la revendication 1, dans lequel l'amine est choisie dans le groupe constitué par la méthylamine, l'éthylamine, la propylamine, la cyclohexylamine, la diméthylamine, la diéthylamine, la dipropylamine, la pipéridine, la morpholine, la triméthylamine, la triéthylamine, 1e tripropylamine,

l'hydroxyde de tétraméthylammonium, l'hydroxyde de tétraéthylammonium et l'hydroxyde de tétrapropylammonium.

Patentansprüche

1. Verfahren zur Herstellung von (6R)-Tetrahydro-L-biopterin, umfassend: das Hydrieren von L-erythro-Biopterin oder einem Acylderivat desselben in Gegenwart eines Amins oder einer quaternären Ammoniumverbindung, die nicht das Biopterin-Ausgangsmaterial ist, welche den pH des Reaktionsmediums auf einen Bereich von 10 bis 13 einstellt, und in Gegenwart eines Hydrierungskatalysators auf Platinbasis bei einem H_2-Druck von 0,981 bar (1 kg/cm²) oder mehr, und für den Fall, daß mindestens eine Acylgruppe in dem erhaltenen hydrierten Biopterinprodukt zurückgeblieben ist, die Entfernung der Acylgruppe durch Hydrolyse.

2. Verfahren gemäß Anspruch 1, wobei die Hydrierung unter einem erhöhten Druck von 10 bis 100 kg/cm² durchgeführt wird.

3. Verfahren gemäß Anspruch 1, wobei der Katalysator auf Platinbasis ausgewählt ist aus der Gruppe, bestehend aus Platinschwarz, Platinoxid, Platin/Kohlenstoff und Platin/Aluminiumoxid.

5. Verfahren gemäß Anspruch 1, wobei die Hydrierung in Wasser durchgeführt wird.

6. Verfahren gemäß Anspruch 1, wobei die Hydrierung bei einer Temperatur in einem Bereich von -10° C bis 50° C durchgeführt werden.

7. Verfahren gemäß Anspruch 1, wobei die Hydrolyse mit Chlorwasserstoffsäure durchgeführt werden.

8. Verfahren gemäß Anspruch 1, wobei das Amin ausgewählt ist aus der Gruppe, bestehend aus Methylamin, Ethylamin, Propylamin, Cyclohexylamin, Dimethylamin, Diethylamin, Dipropylamin, Piperidin, Morpholin, Trimethylamin, Triethylamin, Tripropylamin, Tetramethylammoniumhydroxid, Tetraethylammoniumhydroxid und Tetrapropylammoniumhydroxid.